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| 10/520,169 | 04/27/2005 | Andrew David Bacon | Q85454 | 9237 |

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MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

| EXAMINER | |
|---|---|
| CHEN, SHIN LIN | |
| ART UNIT | PAPER NUMBER |
| 1632 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/520,169 | BACON ET AL. | |
| | Examiner | Art Unit | |
| | Shin-Lin Chen | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *13,16 and 25-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,16 and 25-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-25-08 has been entered.

Applicants' amendment filed 7-25-08 has been entered. Claims 13, 16 and 29 have been amended. Claim 31 has been added. Claims 13, 16 and 25-31 are pending and under consideration.

***Claim Objections***

2. Claim 13 is objected to because of the following informalities: The phrase "which composition comprises liposomes…" in line5 of claim 13 appears to be uncertain of which composition is intended. Changing the phrase to "wherein said composition..." would be remedial. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 13, 16 and 25-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "co-encapsulating said nucleic acid and said assistor protein" in line7 and the phrase "assistor protein in antigenic form is displayed on the surface of the liposomes" in line 12 of claim 13 appear to be in conflict to each other and renders the claim indefinite. The term "encapsulate" means to incase in or to enclose in, or as if in a capsule. Therefore, the assistor protein is "inside" a capsule. However, the phrase "assistor protein in antigenic form is displayed on the surface of the liposomes" appear to mean that the assistor protein is "outside" the capsule, i.e. liposome. It is unclear how the assistor protein can be encapsulated in the liposome and also displayed on the surface of the liposome at the same time. Claims 16, 25-28 and 31 depend from claim 13 but fail to clarify the indefiniteness.

The phrase "co-encapsulating a nucleic acid encoding an influenza hemagglutinin (HA) antigenic protein and influenza HA protein" in lines 3-5 and the phrase "influenza HA protein in antigenic form is displayed on the surface of the liposomes" in line 8 of claim 29 appear to be in conflict to each other and renders the claim indefinite. The term "encapsulate" means to incase in or to enclose in, or as if in a capsule. Therefore, the influenza HA protein is "inside" a capsule. However, the phrase "influenza HA protein in antigenic form is displayed on the surface of the liposomes" appear to mean that the influenza HA protein is "outside" the capsule, i.e. liposome. It is unclear how the influenza HA protein can be encapsulated in the liposome and also displayed on the surface of the liposome at the same time. Claim 30 depends from claim 29 but fail to clarify the indefiniteness.

5. Claim 31 recites the limitation "said liposome-performing components" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 31 depends from claim 13 but there is no "liposome-performing components" recited in claim 13.

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 13, 16 and 25-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Craig, et al., 1997 (WO 97/28818) in view of Gregoriadis et al., 1999 (Methods, Vol. 19, p. 156-162, IDS), Nagy et al., 2007 (US Patent No. 7,285,289 B2) and Gregoriadis et al., 2006 (US Patent No. 7,008,791 B1, '791).

Claims 13, 16, 25-31 are directed to a method of generating an immune response in a mammal by administering to the mammal a liposomal composition comprising a nucleic acid and an assistor protein from an infectious agent, wherein said nucleic acid encodes an antigenic protein, such as influenza hemagglutinin (HA), or portion thereof which shares at least one epitope with said antigenic protein and the liposomes have an average diameter in the range of

100-2000 nm, and the assistor protein is displayed on the surface of the liposome and the liposome lack any further cell targeting moiety, The liposomes include at least one cationically charged component, wherein the nucleic acid and the assistor protein are present in a weight ratio of 1000:1 or 1:1, and the immune response comprises an antibody response. Claims 16 and 28 specify said infectious agent is an infectious virus and influenza virus, respectively. Claim 25 specifies the antigen protein is derived from Hepatitis virus. Claim 26 specifies the liposomes have an average diameter in the range of 100-400 nm. Claim 27 specifies the liposome lack phospholipids. Claim 31 specifies the liposome-performing components include phospholipids.

Craig teaches administering a mixture to a mammal to elicit an immune response in said mammal, wherein the mixture includes a nucleic acid encoding a first epitope and a peptide containing a second epitope such that both of the nucleic acid and the second epitope are taken up by the antigen presenting cell of the mammal (e.g. abstract). Craig teaches that the first and second epitopes are preferably epitopes from the same antigen, and they may comprise the same immuno-dominant epitope from an infectious agents, such as the influenza virus (e.g. p. 4, lines 25-35, claims 24-30). Craig teaches "[i]n the simplest form, the peptide antigen and the nucleic acid encoded antigen described here are the same" (e.g. p. 17, lines 4-5). Craig teaches non-viral delivery means to deliver nucleic acid and an antigenic peptide or protein associated with nucleic acid to a mammal cell, wherein the non-viral delivery means include DNA/polycation complexes, self assembling virus like particles, and microsphere which are used for delivery of DNA or protein to cells, e.g. polyactide glycolide polymers, and **liposomes** (e.g. p. 12, lines 10-25). Craig teaches delivering a nucleic acid encoding an antigenic protein and a peptide antigen via liposome and states that "it is believed that a more effective immune response may be

obtained using a first peptide antigen in combination with a second different nucleic acid-encoded antigen, or wherein several different peptide antigen are administered in combination with one or several different nucleic acid-encoded antigens. A "more effective" immune response will be evidence, as it relates to prior art vaccination procedures and compositions, as two-fold and preferably a five-fold to ten-fold higher immune response, or by the finding that both a cellular and a humoral immune response is elicited by complexes or mixtures of the invention" (e.g. p. 17, lines 4-18). Craig further teaches the ratio of the nucleic acid encoding a first epitope to the amino acid sequence encoding the second epitope could be in the range of 1:10,000 to 1000:1 (e.g. p. 25, last paragraph).

Craig does not specifically teach the antigenic protein displayed on the surface of liposomes, the liposome include at least one cationically charged component or the liposome lack phospholipid, and the average diameter of the liposomes as recited in the claims.

Gregoriadis teaches that liposomes are carriers of peptide, protein and DNA vaccines. Gregoriadis teaches techniques that can generate liposomes of various sizes containing soluble antigens as well as antigen-encoding DNA vaccine (e.g. abstract). Liposomes are usually made up of phospholipids or other amphiphiles, such as nonionic surfactants (e.g. p. 157, bridging left to right column). Gregoriadis also teaches that the average size of the liposome could be in the range from about 100 nm to several micrometers under conditions that preserve the activity of labile drugs (e.g. p. 158, left column). "The number of cycles used depends on the vesicle size required (Table 3) or the sensitivity of the entrapped vaccine (e.g. plasmid DNA) (e.g. p. 160, left column). In table 3, the average size of vaccine-containing DRV liposomes is from 101.9 nm in diameter to 473.9 nm in diameter.

Nagy teaches encapsulating cytokine within a polymerized liposome nanoparticle along with surface display of tumor specific antigen. The arrangement of such surface displayed tumor antigens could easily be optimized for the immune response desired (e.g. column 26, 2nd paragraph).

'791 teaches preparation of oral vaccines comprising cationic liposomes and, complexed or entrapped within the liposomes, a gene vaccine, that is a nucleic acid encoding for an antigen against which vaccination is desired (e.g. column 1, 1st paragraph). The liposome forming components include at least one cationic compound and at least one zwitterionic phospholipid (e.g. column 1, lines 36-57, claim 1).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to display an antigenic protein on the surface of a liposome because Nagy teaches displaying tumor specific antigen on polymerized liposome nanoparticle to stimulate desired immune response in a host. It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to prepare cationic liposomes encapsulating gene vaccine and antigen protein because Craig teaches preparing a liposome containing both gene vaccine and antigenic protein and '791 teaches using cationic compound and zwitterionic phospholipid to produce cationic liposome encapsulating gene vaccine. It also would have been obvious for one of ordinary skill in the art at the time of the invention to produce vaccine-containing liposomes with a diameter in the range of 100-2000 nm or 100-400 nm because Craig teaches using liposome for delivery of a vaccine composition containing both nucleic acid and antigenic protein and Gregoriadis teaches producing vaccine-containing DRV liposomes with a diameter in the range from 101.9 nm to 473.9 nm or from 100 nm to several micrometers, which overlaps

with the recited range of 100-2000 nm or 100-400 nm of the instant invention. Gregoriadis teaches that liposomes are usually made up of phospholipids or other amphiphiles, such as nonionic surfactants. Amphiphiles includes non-phospholipids, such as sodium dodecyl sulfate, Benzalkonium chloride, Cocamidopropyl betaine and octanol (long chain alcohol, non-ionic). Therefore, Gregoriadis teaches preparing liposomes lacking phospholipids and it would be obvious to one of ordinary skill.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to elicit an immune response in a mammal as taught by Craig, to preserve the activity of labile drugs and use liposome as carrier of vaccine as taught by Gregoriadis or to optimize desired immune response as taught by Nagy with reasonable expectation of success.

Applicants argue that Craig suggests immunoliposomes by absorbing immunoglobulin on the liposome surface, however, the instant invention recite liposome lacking further cell targeting moiety (amendment, p. 8). This is not found persuasive because of the reasons or record and the reasons set forth above under 35 U.S.C. 103(a) rejection. Using immunoliposome is only one of the options taught by Craig. Craig does teach non-viral delivery means to deliver nucleic acid and an antigenic peptide or protein associated with nucleic acid to a mammal cell, wherein the non-viral delivery means include DNA/polycation complexes, self assembling virus like particles, and microsphere which are used for delivery of DNA or protein to cells, e.g. polyactide glycolide polymers, and liposomes. One of ordinary skill in the art would know how to prepare

liposomes containing a nucleic acid and an antigenic protein associated with nucleic acid without adding any further targeting moiety on the liposomes in view of the teaching of Craig.

Applicants argue that Craig and Gregoriadis do not teach 10 the nucleic acid is trapped in the intravascular space, 2) the protein displayed on its surface in the absence of a targeting agent and 3) the presence of a cationic liposome component successfully enhance the immune results obtained the this combination. Applicants further argue that Gregoriadis does not teach liposomes lacking phospholipid and the PEG6000 is used in a volume reduction method (amendment, p. 8-9). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 103(a) rejection and that Gregoriadis does teach that liposomes are usually made up of phospholipids or other amphiphiles, such as nonionic surfactants. Amphiphiles includes non-phospholipids, such as sodium dodecyl sulfate, Benzalkonium chloride, Cocamidopropyl betaine and octanol (long chain alcohol, non-ionic). Therefore, Gregoriadis teaches preparing liposomes lacking phospholipids and it would be obvious to one of ordinary skill.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

/Shin-Lin Chen/

Primary Examiner, Art Unit 1632